Development and deployment of new TB drugs

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Declarations

Academic co-ordinator of the PreDiCT-TB consortium

Member of WHO Taskforce on Development of New Tuberculosis Drugs

Co-PI on HIRIF trial (NIH)

Steering committee member RIFAQUIN Trial

DSMB Chair RIFATOX trial
Overview

- A changing landscape
- Rifamycin optimisation
- Fluoroquinolones
- Bedaquiline
- Delaminid
- The (near) future
A short history of Short Course Chemotherapy

THE LANCET, NOVEMBER 9, 1974
CONTROLLED CLINICAL TRIAL OF FOUR SHORT-COURSE (6-MONTH) REGIMENS OF CHEMOTHERAPY FOR TREATMENT OF PULMONARY TUBERCULOSIS
SECOND EAST AFRICAN / BRITISH MEDICAL RESEARCH COUNCIL STUDY

N=953
~240 per arm

THE LANCET, AUGUST 12, 1978
CONTROLLED CLINICAL TRIAL OF FIVE SHORT-COURSE (4-MONTH) CHEMOTHERAPY REGIMENS IN PULMONARY TUBERCULOSIS
First Report of 4th Study
EAST AFRICAN AND BRITISH MEDICAL RESEARCH COUNCILS

N=696
~130 per arm
The Challenge of Resistance

Collaborative meta-analysis of 6724 patients on individualised regimens from 26 centres

<table>
<thead>
<tr>
<th>Condition</th>
<th>Treatment Success (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDR-TB</td>
<td>64</td>
</tr>
<tr>
<td>MDR-TB+I</td>
<td>56</td>
</tr>
<tr>
<td>MDR-TB+Q</td>
<td>48</td>
</tr>
<tr>
<td>XDR-TB</td>
<td>40</td>
</tr>
</tbody>
</table>

Falzon D Eur Resp J 2013 42 : 156-168
New anti-tuberculosis drugs

Rifabutin

Levo/ofloxacin

Protomanid (PA-824)

Rifapentine

Moxifloxacin

Delamanid (OPC-67683)

Gatifloxacin

Bedaquiline (TMC-207)
Efficacy endpoints in TB trials

* Treatment failure may occur with or without development of new resistance

- Death
- 2-month culture conversion
- Time to culture conversion
- Time to failure
- Failure*
- Cure
- 2-month culture conversion
- Time to culture conversion
- Time to failure
- Failure*
- Cure

Re-infection
Early relapse
Late relapse
Recurrence
Time to relapse

Limit of Detection

Davies G Tuberculosis 2010 90:171-6
Rifamycins: Phase II trials

TBTC Study 29
- $2P_{10}HZE$
- $2P_{10}HZE$
- $2P_{15}HZE$
- $2P_{20}HZE$
- $2R_{10}HZE$
- $2R_{15}HZE$
- $2R_{20}HZE$
- $2R_{40}HZE$

TBTC Study 29X
- $2P_{10}HZE$
- $2P_{15}HZE$
- $2P_{20}HZE$
- $2R_{10}HZE$
- $4R_{10}H$

PanACEA HR2
RIFATOX
HIRIF

PanACEA HR1
MAMS
Rifamycins: Phase II Trials

Study 29 (P10) (N=444)
Study 29X (P10) (N=169)
Study 29X (P15) N=164
Study 29X (P20) N=164
RIFATOX (R15) N=176
RIFATOX (R20) N=187
HIGHRIF (R15) N=95
HIGHRIF (R20) N=95

Difference in proportion culture positive at 2 months (%)

Favours Control

Favours Active

-26.4 -3.3 19.7 27.3
-23.2 10.5 24.9
-21.0 13.4 24.9
-19.9 8.3 21.0
-15.9 6.3 27.3
-11.2 3.7 11.0
-9.0 3.7 11.0
-4.1 8.1 19.9
8.1 5.0 23.2
8.3 23.2
5.3 3.3 23.2
0.9 3.7 11.0
3.3 11.2 23.2
3.7 11.0 23.2

Favours Control
Rifamycins: PK and Safety

- Saturable and non-linear PK observed for RIF
- Decreasing bioavailability with dose and food effect with RP
- Grade 3 transaminitis/hepatitis 2-4%
- No reports of immune-mediated syndromes
- HR1 MTD Study up to 40 mg/kg
- PanaCEA MAMS Study
# Fluoroquinolones: Phase II Trials

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Fluoroquinolone (FQ)</th>
<th>Basic regimen</th>
<th>Risk Ratio</th>
<th>M.H. Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1.5.1 Ciprofloxacin vs rifampicin</strong></td>
<td></td>
<td></td>
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<tr>
<td>Morbity 1993</td>
<td>27</td>
<td>30 25</td>
<td>11.9%</td>
<td>1.00 [0.88, 1.22]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>30</td>
<td>30 25</td>
<td>11.9%</td>
<td>1.00 [0.88, 1.22]</td>
</tr>
<tr>
<td>Total events</td>
<td>27</td>
<td>25</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Heterogeneity: Not applicable</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.76 (P = 0.45)</td>
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</tr>
</tbody>
</table>

| 1.5.2 Ciprofloxacin vs ethambutol plus pyrazinamide | | | | |
| Kennedy 1993 | 6 | 9 11 | 3.0% | 0.58 [0.42, 1.09] |
| Subtotal (95% CI) | 9 | 11 11 | 3.0% | 0.58 [0.42, 1.09] |
| Total events | 6 | 11 | | |
| **Heterogeneity: Not applicable** | | | | |
| Test for overall effect: Z = 1.62 (P = 0.11) | | | | |

| 1.5.3 Ofloxacin versus ethambutol | | | | |
| Kohne 1992 | 40 | 52 49 | 63 13.0% | 0.86 [0.61, 1.11] |
| Rustonjee 2006b | 28 | 50 32 | 50 5.7% | 0.59 [0.39, 1.11] |
| Subtotal (95% CI) | 115 | 112 112 | 18.7% | 0.94 [0.80, 1.10] |
| Total events | 76 | 91 | | |
| **Heterogeneity: Tau² = 0.05; CH² = 6.67; df = 1 (P = 0.35); I² = 0%** | | | | |
| Test for overall effect: Z = 0.75 (P = 0.45) | | | | |

| 1.6.4 Levofloxacin addition | | | | |
| El-Said 1996 | 46 | 53 64 | 62 15.9% | 1.11 [0.95, 1.30] |
| Subtotal (95% CI) | 53 | 62 62 | 15.9% | 1.11 [0.95, 1.30] |
| Total events | 46 | 64 | | |
| **Heterogeneity: Not applicable** | | | | |
| Test for overall effect: Z = 1.34 (P = 0.18) | | | | |

| 1.6.5 Gatifloxacin versus ethambutol | | | | |
| Rustonjee 2006b | 40 | 52 32 | 50 8.4% | 1.20 [0.93, 1.55] |
| Subtotal (95% CI) | 52 | 52 50 | 8.4% | 1.20 [0.93, 1.55] |
| Total events | 40 | 32 | | |
| **Heterogeneity: Not applicable** | | | | |
| Test for overall effect: Z = 1.41 (P = 0.16) | | | | |

| 1.6.6 Moxifloxacin vs ethambutol | | | | |
| Burman 2005 | 89 | 159 93 | 167 13.0% | 1.00 [0.83, 1.19] |
| Corde 2009 | 69 | 55 45 | 65 9.0% | 1.21 [1.02, 1.46] |
| Rustonjee 2006b | 36 | 44 32 | 39 8.7% | 1.26 [1.01, 1.59] |
| Subtotal (95% CI) | 280 | 362 362 | 31.2% | 1.17 [0.96, 1.41] |
| Total events | 184 | 173 | | |
| **Heterogeneity: Tau² = 0.01; CH² = 4.19; df = 2 (P = 0.12); I² = 62%** | | | | |
| Test for overall effect: Z = 1.62 (P = 0.10) | | | | |

| 1.6.7 Moxifloxacin vs isoniazid | | | | |
| Dornan 2006 | 69 | 219 90 | 214 10.0% | 1.07 [0.97, 1.19] |
| Subtotal (95% CI) | 219 | 214 214 | 10.0% | 1.07 [0.97, 1.19] |
| Total events | 69 | 90 | | |
| **Heterogeneity: Not applicable** | | | | |
| Test for overall effect: Z = 0.66 (P = 0.51) | | | | |

| Total (95% CI) | 776 | 801 100.0% | 1.07 [0.98, 1.17] |
| Total events | 489 | 478 | | |
| **Heterogeneity: Tau² = 0.01; CH² = 12.07; df = 9 (P = 0.16); I² = 31%** | | | | |
| Test for overall effect: Z = 1.56 (P = 0.11) | | | | |
| Test for subgroup differences: CH² = 7.94; df = 6 (P = 0.24); I² = 24.6% | | | | |

Zigansina L, Titarenko A, Davies GR. Cochrane Database of Systematic Reviews update 2013
Fluoroquinolones: Phase III trials

- **RIFAQUIN**
  - HRZE
  - HRZM
  - HRZM
  - HRZE
  - HR
  - HP_{15} 1w
  - HP_{20} 2w

- **OFLOTUB III**
  - HRZE
  - HRZG
  - HRZG
  - HRZE
  - HR

- **REMox-TB**
  - HRZE
  - HRZM
  - MRZE
  - HRZM
  - HR

**Timeline:**
- Months: 0, 2, 4, 6
Fluoroquinolones: Phase III Trials

RIFAQUIN
2HRZM/2HP
n=593

RIFAQUIN
2HRZM/4HP
n=593

OFLOTUB-III
2HRZG/2HR
n=917

REMox
2HRZM/2HR
n=524

REMox
2MRZE/2HR
n=514

Difference in Unfavourable Outcome (%)

Favours Active  NI δ  Favours Control

-4.7  0.4  6.8  13.1  19.4
-0.03  3.8  5.6  8.00
3.8  9.0  14.2
2.7  7.8  13.0
Bedaquiline: pharmacology

- Target $atpE$ subunit of ATP synthase
- Bioavailability 2x with food
- Protein-binding >99%
- Metabolised by CYP3A4, AUC $\downarrow$ 50% RIF, $\uparrow$ 2-3x RTV
- Inactive monodesmethyl metabolite (M2)
- Complex PK/dosing with loading and terminal $t_{1/2}$ 5.5 months

Andries K 2005 Science 307: 223-7
Bedaquiline: Efficacy

**C208 Stage 2:**
Time to Culture Conversion (Wk 24 – mITT)

Primary endpoint (difference in TtC):
\[ p = \leq 0.0001 \]

- **BDQ/BR (N=58)**: 58, 37, 25, 12, 7, 3
- **Placebo/BR (N=56)**: 51, 53, 40, 30, 22, 5

Median time to culture conversion was 12 weeks in the BDQ group and 18 weeks in the placebo group.

p-value from Cox proportional model adjusting for strata

*FDA NDA 204-384 Briefing package November 2012*
Bedaquiline: Safety

- 12.7% vs 2.5% mortality in C208 trial (p=0.017)
- QTcF prolongation in 26.4% vs 7.7% but no cardiac events
- Conditionally approved with a black-box warning
- WHO guidance recommended informed consent and active pharmacovigilance
- Stronger evidence for early use in MDR-TB then XDR-TB
Delamanid: pharmacology

- Target mycolic acid synthesis
- Prodrug substrate for nitroreductases (Rv3547 and F₄₂₀ system)
- Bioavailability 4x with food
- Protein binding >99.5%
- Primary metabolism by albumin amino groups, 8 inactive metabolites
- Some CYP Interaction AUC ↓ 52% RIF, ↑ 20% RTV
- Twice daily dosing with terminal $t_{1/2}$ 32 hours
Delamanid : development programme

Trial 204 (2 months)  Intensive Phase (6-8m; >4m post-SCC)

Trial 208 (6 months)  Continuation Phase (12-18m; >16m post-SCC)

Observational Study 116 (24 months)

204 completers enrolled in 116 pending enrollment in 208 after variable delay

WHO OBR

Scripkonoca V Eur Resp J 2013 42 : 1393-400
Delamanid: Efficacy

Trial 204

Sputum culture conversion in MGIT* at 2 months

- OBR + Placebo: 29.6% (37/125)
- 100mg BID: 45.4% (64/141)
- 200mg BID: 41.9% (57/136)

p = 0.039

p = 0.008

* Mycobacteria Growth Indicator Tube

Trial 208

- DLM<= 2m
- DLM>= 6m

Mortality 8.3% versus 1% for <2 and >=6m (p<0.001)

EMA Public Assessment Report EMA/CHMP/125521/2013 December 2013
The (Near) Future

- Effective roll-out of novel regimens to NTPs
- Continued efforts to reach an ultra-short regimen for DS-TB (TBTC Study 31)
- Treatment shortening to 9m for MDR-TB (STREAM)
- Completion of Phase III trials for BDQ and DLD (STREAM/ C210, Otsuka 213)
- Evaluation of new drugs in the DS-TB context (NC001-5)
- Promise of Phase III trials of universal regimens (STAND)